Received: 18 July 2023 | Accepted: 23 August 2023
DOI: 10.1002/psp4.13050

ARTICLE

Population PK/PD modeling of low-density lipoprotein cholesterol response in hypercholesterolemic participants following administration of bococizumab, a potent anti-PCSK9 monoclonal antibody

Ellen Q. Wang[1] | **Nitin Kaila**[2] | **David Plowchalk**[2] | **Leonid Gibiansky**[3] | **Carla Yunis**[4] | **Kevin Sweeney**[2]

[1]Clinical Pharmacology & Bioanalytics, Pfizer Inc., New York, New York, USA
[2]Clinical Pharmacology & Bioanalytics, Pfizer Inc., Groton, Connecticut, USA
[3]QuantPharm LLC, North, Maryland, USA
[4]Global Product Development, Pfizer Inc., Florida, USA

Correspondence
Ellen Q. Wang, Clinical Pharmacology & Bioanalytics, Pfizer Inc., 66 Hudson Boulevard East, New York, NY 10001, USA.
Email: ellen.q.wang@pfizer.com

Abstract
We sought to characterize the population pharmacokinetic/pharmacodynamic (PK/PD) relationship of bococizumab (RN316/PF-04950615), a humanized IgG2Δa monoclonal antibody that binds to secreted human proprotein convertase subtilisin kexin type 9 (PCSK9), using data derived from 16 phase I, II, and III clinical studies (36,066 bococizumab observations, 46,790 low-density lipoprotein cholesterol [LDL-C] measurements, 3499 participants). A two-compartment disposition model with parallel linear and Michaelis–Menten elimination and an indirect response model was used to characterize the population PK and LDL-C response of bococizumab. Potential model parameters and covariate relationships were explored, and visual predictive checks were used for model assessment and validation. Key covariates included the effect of anti-drug antibodies (ADAs) on exposure through impact on clearance and bioavailability; impact of statins on bococizumab elimination (maximal rate of metabolism); and impact of statins, Asian race, and male sex on LDL-C efficacy (maximum effect). ADAs and neutralizing ADAs did not have additional effects on LDL-C beyond the influence on bococizumab exposure. In conclusion, the population PK/PD model adequately describes bococizumab concentration and LDL-C efficacy. The covariate effects are consistent with the presumed mechanism of action of PCSK9 inhibitors. With increasing availability of antibody-based therapeutics, improved understanding of the effect of ADAs and statins on bococizumab PK/PD adds to the literature and enhances our pharmacological understanding of how immunogenicity and concomitant medications may impact the PK/PD of biotherapeutics.

ClinicalTrials.gov identifiers: NCT00991159; NCT01163851; NCT01435382; NCT01243151; NCT02043301; NCT02458209; NCT01342211; NCT01350141; NCT01592240; NCT02055976; NCT01968954; NCT01968967; NCT01968980; NCT02100514; NCT02135029; and NCT02458287.

Nitin Kaila, David Plowchalk and Kevin Sweeney worked in Clinical Pharmacology & Bioanalytics, Pfizer Inc. at the time of this study.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Population pharmacokinetic/pharmacodynamic (PK/PD) modeling is commonly used to describe the PK/PD relationship of investigational drugs, including monoclonal antibodies (mAbs). As with all biologics, there is potential for immunogenicity to impact PK, PD, efficacy, and/or safety of a mAb.

WHAT QUESTION DID THIS STUDY ADDRESS?

We characterized the PK/PD relationship of an anti-PCSK9 mAb, bococizumab, and estimated the impact of intrinsic and extrinsic covariates, including anti-drug antibodies (ADAs), on bococizumab PK/PD relationship.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

A two-compartment model with parallel linear and nonlinear Michaelis–Menten elimination and an indirect response model adequately described the observed bococizumab concentration data and LDL-C reduction. While the impact of ADAs and neutralizing antibodies on PK/PD was explored, increased bococizumab clearance due to ADAs was identified as the factor impacting observed changes in bococizumab concentrations and LDL-C response over time. Statin therapy increased bococizumab elimination and LDL-C efficacy.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

With increasing availability of antibody-based therapeutics, understanding the effect of ADAs and statins on the PK/PD of bococizumab provides important information on how immunogenicity and concomitant medication can be incorporated in PK/PD analysis to enhance the understanding of the influence of immunogenicity and other covariates on the PK/PD of biotherapeutics.

INTRODUCTION

Bococizumab is a humanized IgG2Δa monoclonal antibody (mAb) that binds to secreted human proprotein convertase subtilisin kexin type 9 (PCSK9) with high affinity, effectively preventing it from binding to low-density lipoprotein receptors (LDL-Rs).[1] LDL-Rs are largely responsible for the clearance of low-density lipoprotein cholesterol (LDL-C),[2] and when PCSK9 binds to LDL-R it promotes degradation of the receptor.[3] By antagonizing PCSK9, anti-PCSK9 mAbs increase expression of LDL-R, leading to increased LDL-C clearance and reduced concentration of LDL-C in circulation.[4,5] Circulating PCSK9 concentrations appear to be positively correlated with atherogenic lipoproteins,[6] and there is also evidence to suggest that PCSK9 accelerates atherosclerosis and coronary artery disease by several mechanisms that are independent of elevated liver LDL-R degradation.[7–9] Thus, PCSK9 plays a central role in the physiology of LDL-C processing,[4,5] and since 2017 anti-PCSK9 mAbs have become a key addition to the pharmaceutical management of LDL-C and atherosclerotic cardiovascular risk.[10]

The safety, efficacy, and pharmacokinetics (PK) of bococizumab were evaluated as part of a clinical development program,[11–20] but global development was discontinued in November 2016 as a result of the emerging profile observed from the Studies of PCSK9 Inhibition and the Reduction of vascular Events (SPIRE) phase III lipid-lowering program.[15,19,21] The SPIRE program reported an unanticipated attenuation of LDL-C lowering over time, alongside a higher incidence of anti-drug antibodies (ADAs), and a higher rate of injection-site reactions compared with other agents in this drug class.[15] More specifically, 48% of participants in the SPIRE lipid-lowering studies had detectable ADAs to bococizumab and 29% also developed neutralizing antibodies (NAbs).[15] The SPIRE studies also showed a titer-dependent decrease in bococizumab exposure and attenuation in PCSK9 response and LDL-C lowering. In addition, in participants whose maximum ADA titer was in the highest 10th percentile, LDL-C response was close to that of placebo participants, whereas participants whose titers were in the lowest two-thirds of maximum titer (<1:1176) had an LDL-C response similar to that of participants who were ADA negative.[15] Similar conclusions were reached when bococizumab exposure, PCSK9 response, and LDL-C data were analyzed by NAb titer. A high incidence of ADAs has not been reported for the two approved PSCK9 inhibitors – alirocumab and evolocumab – currently used in clinical practice to reduce the risk of cardiovascular events and/or as an adjunct to diet and other lipid-lowering therapies in patients with hyperlipidemia, including heterozygous familial hypercholesterolemia,[22,23] although patients who developed ADAs to alirocumab have a higher rate of injection-site reactions than patients who were ADA negative (10.2% vs. 5.9%).[22]

The clinical impact of ADAs and/or NAbs on bococizumab PK, pharmacodynamics (PD), and efficacy is not unique: all biologics have the potential to be immunogenic, particularly with repeated dosing, and although humanization reduces the risk of an immune response, the potential for immunogenicity still exists for both humanized and fully human antibodies.[24–27] Indeed, the development of ADAs to adalimumab, a fully human antitumor necrosis factor (TNF) mAb, is well-reported.[28,29] For example, Bartelds et al. reported a decreased serum concentration and reduced efficacy for adalimumab in a long-term follow-up study of 272 patients with rheumatoid arthritis.[30] Similar impact of ADAs on the efficacy and serum concentration of adalimumab has been reported for patients treated with this anti-TNF mAb for inflammatory bowel disease[31] and for psoriasis.[32] In a review by Wang et al., the authors report that of the 121 approved biologic products, 89% ($n=108$) reported ADA incidence, whereas only 49% ($n=59$) included information on whether or not immunogenicity had an impact on efficacy and an even smaller percentage (26%; $n=31$) included information on the PK of the biologic product.[27] This highlights a real gap in the literature when reporting the impact of immunogenicity on PK and ultimately the efficacy response to biotherapeutics.

The objective of the present analysis was to characterize the population PK of bococizumab and the relationship between bococizumab concentration and LDL-C response, and to estimate the impact of intrinsic (e.g., age, sex, body weight, race, etc.) and extrinsic covariates (e.g., ADAs and statin therapy) on bococizumab PK and PK/PD relationship using data from completed bococizumab clinical studies.

METHODS

Population PK/PD database

A PK/PD database was built using data derived from 16 studies, either phase I (NCT00991159; NCT01163851 NCT01435382; NCT01243151; NCT02043301; and NCT02458209),[13,16,17] phase II (NCT01342211; NCT01350141; NCT01592240; and NCT02055976),[11,12,18] or phase III bococizumab clinical studies (NCT01968954; NCT01968967; NCT01968980; NCT02100514; NCT02135029; and NCT02458287),[14,15,33] following either single or multiple dose (weekly, every-2-week [q2w], or every-4-week [q4w] schedules), via intravenous (i.v.) or subcutaneous (s.c.) administration, and of various weight proportional (0.25 to 18 mg/kg i.v.) or flat (50–300 mg s.c.) bococizumab doses. Dense PK/PD samples were collected from six phase I, and three phase II studies,[12,13,16–18] whereas sparse PK/PD samples were collected from one phase IIb and six phase III studies (mostly trough samples).[11,14,15,33] Immunogenicity assessments were done regularly in phase II and III studies. Primary observations from these clinical studies have been presented in full elsewhere.[11–18]

All studies included in this pooled analysis were conducted in compliance with ethical standards outlined by the Declaration of Helsinki. All protocol documents were reviewed and approved by the relevant institutional review board or independent ethics committee. All participants provided written, informed consent. Full detail is given in the primary publications.[11–18]

Data captured included subject identification (unique study ID and study number), demographic characteristics (age, sex, body weight, body mass index [BMI], sex, and race), laboratory values (baseline LDL-C level and calculated creatinine clearance), concomitant statin medication (e.g., atorvastatin, simvastatin, and rosuvastatin), observed bococizumab and postdose LDL-C concentrations, and dosing information (route, date and time of each planned dose, and actual dose received). In addition, fractions of the PK measurements below the lower limit of quantification (<LLOQ) were flagged. ADAs and NAbs were measured, and the dataset contained both time-independent (same for all times for each patient: missing or yes/no) and time-dependent characterization of these assessments. To create time-dependent ADA variables, available ADA measurements were linearly (in time) interpolated between the observed titer values.

Total bococizumab concentration, total PCSK9 concentration, ADA, and NAb were measured using validated assays (described in full elsewhere[15]).

Software

The population PK/PD analyses were conducted via nonlinear mixed-effects modeling with NONMEM software, version 7.4.1 (ICON Development Solutions). Graphical and all other statistical analyses, including evaluation of NONMEM outputs, were performed using R version 3.3.3 for Windows (R project, http://www.r-proje ct.org/). The first-order conditional estimation with INTERACTION option method in NONMEM was used for all model runs.

Base model development approach

Structural PK/PD model development was driven by data and based on goodness-of-fit indicators, including visual inspection of diagnostic plots, plausibility and precision of the parameter estimates, minimum objective function value, and number of estimated parameters. Potential covariate–parameter relationships were selected based on exploratory graphics and mechanistic considerations, added simultaneously to the full model. The final base and covariate models were evaluated by constructing a series of graphical evaluation plots and visual predictive checks (VPCs).

Population PK/PD model development

Based on previous modeling efforts,[34,35] a two-compartment disposition model with parallel nonspecific (linear) and target-mediated (Michaelis–Menten [MM]) elimination and first-order s.c. absorption was used to describe bococizumab PK following i.v. and s.c. administration. In addition, the effect of bococizumab on LDL-C reduction was defined by an indirect response model.[36] As the current dataset includes multiple large phase III studies,[14,15] several additional PK/PD models were explored which included quasi-steady-state approximation of target-mediated drug disposition, MM disposition with indirect LDL-C response (inhibition of LDL-C production or stimulation of LDL-C elimination), and a mechanistically consistent interaction model including LDL-R stimulation. In addition, the effects of ADAs on bococizumab PK/PD were explored.

Interindividual variability in the PK parameters (i.e., clearance [CL] and central compartment volume of distribution [V_c]) were modeled using multiplicative exponential random effects of the form, according to Equation 1:

$$\theta_i = \theta \bullet e^{\eta_i} \tag{1}$$

where θ is the typical population mean value of the parameter (e.g., CL, V_c, or peripheral compartment volume of distribution [V_p]) and η_i denotes the interindividual random effect accounting for the ith individual's deviation from the typical value having zero mean and variance (ω^2). The approximate percent coefficient of variation (%CV) was calculated according to Equation 2:

$$\%\mathrm{CV} = \sqrt{\omega^2} \times 100\,\% \tag{2}$$

A proportional error model or combined (additive + proportional) error model was considered for residual variability. Other residual error models were explored if heterogeneity was observed in the conditional weighted residual (CWRES) versus predicted (PRED) or individual weighted residual (IWRES) versus individual predicted (IPRED) plots.

Covariate model development

The base model was fitted to the dataset. Initial covariate screening was conducted graphically using Empirical Bayes prediction of the inter-individual random effect plots of normalized covariate values. For covariates that are highly correlated (e.g., body weight, body surface area, and BMI), body weight was preferred unless the reduction in objective function or parameter variability was substantially greater for another covariate. A full model approach was used to test inclusion of intrinsic covariates, including age, sex, body weight, race, statin, other lipid-lowering therapy, and estimated glomerular filtration rate on absorption rate constant, s.c. bioavailability, CL and volume parameters, maximum nonlinear elimination rate (V_{max}), and maximum effect (E_{max}). These covariates were selected as they impart some physiologic, pharmacologic, or mechanistic relevance in the model. In addition to the covariates identified above, additional PD covariates were explored; these included the expected effects of statins on E_{max} and of baseline LDL-C on half maximal effective concentration (EC_{50}), which are expected for anti-PCSK9 mAbs.

The respective impact of ADAs and NAbs on PK and PD (efficacy) of bococizumab were also assessed. The initial focus was the impact of ADA on clearance mechanism, although the inclusion of NAb on efficacy was also explored to assess further improvement in model fit in the event that ADA titer alone as an elimination function did not adequately describe the observed loss in LDL-C response durability. Relevance of the impact was confirmed by the 95% confidence interval (CI) constructed for the ADA clearance parameter(s) excluding the null value.

Full model development

In general, continuous covariates were normalized on a typical reference value and then included in the full model using a power function, as described below. For instance, the change in physiologic parameters, as a function of body weight, is both theoretically[37] and empirically described by an allometric model, according to Equation 3:

$$\mathrm{TVP} = \theta_{\mathrm{TVP}} \bullet \left(\frac{\mathrm{WT}_i}{\mathrm{WT}_{\mathrm{ref}}}\right)^{\theta_{\mathrm{allo}}} \quad (3)$$

where TVP is the typical value of a model parameter; WT_i is the individual body weight; $\mathrm{WT}_{\mathrm{ref}}$ is the reference body weight; θ_{TVP} is an estimated parameter describing the typical PK parameter value for an individual with weight equal to the reference weight; θ_{allo} is a fixed allometric power parameter, which is assigned an initial value of 0.75 for physiologic processes, such as CL, and an initial value of 1 for anatomic volumes. If attempts at estimation are unsuccessful or if the resultant CIs around the estimates include 0.75 and 1 (for CL and volume, respectively), the model may be simplified by fixing those values in subsequent steps.

Categorical covariates were tested using a power model, as described by Equation 4:

$$\mathrm{TVP} = P_{\mathrm{pop}} \bullet \theta^{\mathrm{COV}_i} \quad (4)$$

where TVP is the typical population mean value of the PK parameter with covariate value COV_i, P_{pop} represents the population central tendency for the PK parameter TVP, and θ represents a NONMEM estimated direct proportionality constant conditional on the population of participants with covariate value $\mathrm{COV}_i = 1$.

Final model development and validation

Once the full model was developed, a clinically relevant parsimonious model was determined through bootstrap analysis, which generated 95% CIs for all parameters estimated in the final model. Any CIs for covariate model parameters enclosing the null value justified the covariate being excluded from the final model. Diagnostic plots to assess goodness-of-fit were generated and included, but were not limited to PRED versus observed concentrations (DV), IPRED versus DV, and residual (CWRES and IWRES) plots versus time stratified by dose.

The adequacy of the base and final covariate models (PK and PK/PD) were investigated with a VPC method. Monte Carlo simulations were used to generate 1000 datasets based on the 16 bococizumab studies. The original dataset was compared with the 10th, 50th, and 90th percentiles of the simulated data, stratified by dose, study, and route of administration (s.c. or i.v.). The VPC evaluation focused on the 52-week phase III studies, which were of similar design.[14,15,33] In addition, as immunogenicity is known to impact both the PK and PD of bococizumab, VPCs were stratified for participants who were ADA-negative, ADA-positive participants whose titer was in the lowest and second lowest tertile, top third tertile, and ADA-positive participants with titer in the top 10%, again using data from the 52-week phase III studies.[14,15]

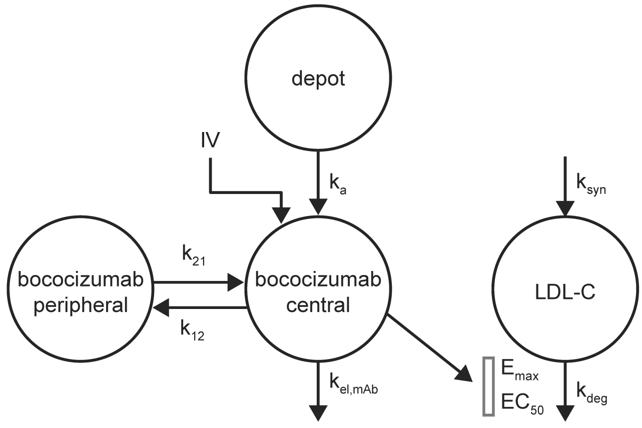

FIGURE 1 Schematic diagram of the population PK/PD model structure. EC_{50}, half maximal effective concentration; E_{max}, maximum effect; IV, intravenous; LDL-C, low-density lipoprotein cholesterol; mAb, monoclonal antibody; PD, pharmacodynamic; PK, pharmacokinetic. All PK/PD parameters are defined within the Methods section.

RESULTS

Summary of dataset

The final PK dataset contained 36,066 bococizumab observations, and 46,790 LDL-C measurements, from 3499 participants, from 16 clinical studies. Covariate characteristics of the dataset are summarized in Table S1. Mean age was 57.3 years, mean body weight 85.8 kg, and mean BMI 30.1 kg/m^2. Baseline LDL-C was (mean ± standard deviation) 125 ± 35.7 mg/dL, and ranged between 28 and 374 mg/dL, encompassing participants with and without familial hypercholesterolemia. The majority of participants received bococizumab via an s.c. route of administration (93.5%), and 39.3% participants had detectable ADAs (at any time during the study). The majority of participants (76.7%) were on concomitant statin therapy.

Base population PK/PD model

A two-compartment PK disposition model with linear and nonlinear elimination and first-order absorption best described the observed bococizumab PK data according to Equations 5–7 (Figure 1). The observed LDL-C response was best described by an indirect response model with LDL-C elimination described by the sigmoid function of bococizumab concentration according to Equation 8:

$$\frac{dA_1}{dt} = -k_a * A_1 \quad (5)$$

$$\frac{dA_2}{dt} = k_a * A_1 - (k_{el} + k_{12}) * A_2 + k_{21} * A_3 - \left[\frac{V\max * A_2}{K_M + A_2/V_C}\right] \quad (6)$$

$$\frac{dA_3}{dt} = k_{12} * A_2 - k_{21} * A_3 \quad (7)$$

$$\begin{aligned} \frac{dLDLC}{dt} &= k_{syn} - k_{deg} LDLC * H(C), \\ H(C) &= 1 + \frac{E_{max} \times C^\gamma}{EC_{50}^\gamma + C^\gamma} \\ LDLC(0) &= \frac{k_{syn}}{k_{deg}} \end{aligned} \quad (8)$$

where A_1, A_2, and A_3 are the bococizumab amounts in the depot, central, and peripheral compartments, respectively; k_a (1/day) is the s.c. absorption rate constant; k_{el} (1/day) is the elimination rate constant; k_{12} and k_{21} are the distribution rate constants; V_{max} (µg/mL/day) is the maximum nonlinear elimination rate; K_M (µg/mL) is the concentration associated with 50% of V_{max}; t is time; the model was parameterized in terms of clearance (CL, L/day), central volume (V_C, L), peripheral volume (V_P, L), and intercompartment clearance (Q, L/day) as follows: $k_{el} = CL/V_C$; $k_{12} = Q/V_C$; $k_{21} = Q/V_P$; k_{syn} is the zero-order production rate of LDL-C; k_{deg} is the first-order elimination rate of LDL-C; $H(C)$ is the function affecting k_{deg}; E_{max} and EC_{50} are the maximum effect and bococizumab concentration associated with 50% of E_{max}; and γ = parameter that controls the shape of the effect curve.

Final population PK/PD model

A parallel linear and MM elimination model was developed, with first-order absorption which was deemed to adequately describe the PK data following i.v. and s.c. dose administration of bococizumab into the central and s.c. dose compartments, respectively. Covariate model development was carried out over several iterations. The final model, based upon the base model outlined above, is described by Equations 9–24. Base model parameters were altered by including the effects of body weight on CL and volume (V_C and V_P); effect of BMI on V_{max} and s.c. bioavailability (F_{SC}); effect of age on k_a and Q; effect of ADA on CL and F_{SC}; and effect of the presence of statin(s) on V_{max}. Additional covariates included in the model included the effect of single-dose studies on bioavailability; and a mixture model that described unexplained and abrupt decreases of bioavailability approaching zero, possibly related to noncompliance.

$$k_a = \theta_1 \bullet \left(\frac{Age}{60}\right)^{\theta_{12}} \bullet e^{\eta_1} \quad (9)$$

$$CL = \theta_2 \bullet \left(\frac{WT}{75}\right)^{\theta_9} \bullet \left(1 + \theta_{20} \bullet e^{(\eta_9 + ADAT1 - 10)}\right) \bullet e^{\eta_2} \quad (10)$$

$$V_C = \theta_3 \bullet \left(\frac{WT}{75}\right)^{\theta_{10}} \bullet e^{\eta_3} \quad (11)$$

$$Q = \theta_4 \bullet \left(\frac{Age}{60}\right)^{\theta_{13}} \bullet e^{\eta_4} \quad (12)$$

$$V_P = \theta_5 \bullet \left(\frac{WT}{75}\right)^{\theta_{11}} \bullet e^{\eta_5} \quad (13)$$

$$V_{max} = \theta_6 \bullet \left(\frac{BBMI}{30}\right)^{\theta_{14}} \bullet \theta_{16}^{STYPCL} \bullet e^{\eta_6} \quad (14)$$

$$K_M = \theta_7 \quad (15)$$

$$F1 = \theta_8 \bullet \theta_{17}^{single} \bullet \left(\frac{BBMI}{30}\right)^{\theta_{15}} \bullet \left[1 + \theta_{21} \bullet e^{(\eta_{10} + ADAT1 - 10)}\right]^{-1} \bullet [1 + F(mixnum, t)]^{-1} \bullet e^{\eta_7} \quad (16)$$

F (mixnum, t) is described by a mixture model with probabilities of

$$p_1 = 1 - \theta_{18}, p_2 = \theta_{18} \quad (17)$$

$$F(1,t) = 0, F(2,t) = (t/T_{50})^5 \quad (18)$$

$$T_{50} = \theta_{19} \bullet e^{\eta_8} \quad (19)$$

$$k_{syn} = \theta_{26} \bullet e^{\eta_{12}} \quad (20)$$

$$k_{deg} = k_{syn}/BLDL \quad (21)$$

$$\gamma = \theta_{27} \quad (22)$$

$$E_{max} = \theta_{28} \bullet \theta_{29}^{STYPCL} \bullet \theta_{30}^{ASIAN} \bullet \theta_{31}^{MALE} \bullet e^{(\eta_{13} + \theta_{32} * \eta_2)} \quad (23)$$

$$EC_{50} = \theta_{33} \bullet \left(\frac{BLDL}{140}\right)^{\theta_{34}} \bullet \theta_{35}^{LOWDOSE} \bullet \left[1 + \frac{\theta_{36} \bullet t}{\theta_{37} + t} \bullet e^{\eta_{15}}\right] \bullet e^{\eta_{14}} \quad (24)$$

where WT is body weight; ADAT1 is a time-dependent ADA titer; *BBMI* is the baseline BMI; *STYPCL* is the presence of statin(s); “single” is single dose; *F1* is bioavailability; BLDL is the baseline LDL-C; LOWDOSE is the 25 mg s.c., 50 mg s.c., or less than or equal to 25 mg i.v. doses; θ_{36}

is the maximum fractional increase in EC_{50} with time; θ_{37} is the time 50% of this effect is observed; mixnum is the NONMEM parameter, mixture number with value of 1 and 2 for populations 1 and population 2, respectively, and T_{50} is the time when bioavailability decreased by a factor of 2 relative to the bioavailability at time 0.

The log-normal between-subject variability was estimated on all parameters except for V_{max} and K_M. The residual error was expressed as a combination of additive and proportional terms with different magnitude for phase I, II, and III studies, and random effect on the magnitude of the residual error. Observations below the LLOQ were included using the M3 method.[38]

The final covariates in the PD model included the effect of statin(s), sex, Asian race, and η_2 on E_{max}, and effect of baseline LDL-C and low dose on $EC_{50.}$ Additionally, effect of time postdose was identified as a covariate on EC_{50}.

Bococizumab final PK and PK/PD parameter estimates

The final PK and PK/PD parameter estimates for bococizumab are shown in Table 1. The s.c. bioavailability (41.1%), linear CL (0.227 L/day), Q (0.335 L/day), V_c (2.38 L), and V_p (1.95 L) parameters for bococizumab were generally consistent with those expected for mAbs. Furthermore, V_{max} (2.04 µg/mL/day) and K_M (12.5 µg/mL) indicated significant nonlinear elimination. In addition, k_a declined with age; F_{SC} decreased with BMI; CL, V_c, and V_p increased with weight; Q decreased with age; the single-dose s.c. bioavailability was higher than the typical population prediction; and V_{max} increased with BMI. Of note, V_{max} was 17.0% higher in participants who were administered statins.

The final PD parameters for bococizumab are also given in Table 1. The indirect response model with stimulation of k_{deg} well-described the observed data. The maximum effect of LDL-C degradation (E_{max}) was higher in participants co-administered statins, higher in male participants and in Asian participants, and was also impacted by the random effect on bococizumab clearance. The fit of the model was further improved when $EC_{50}(t)$ was allowed to change as a function of time, from 3.35 µg/mL at time zero to 4.14 µg/mL at 1 year. EC_{50} increased with baseline LDL-C value and was lower in participants administered low doses of bococizumab (<50 mg s.c. or 25 mg i.v.; Table 1).

The presence of ADAs strongly increased CL and decreased s.c. bioavailability, with the effects proportional to the exponent of the observed ADA titers. It was estimated that for 11.5% of participants with ADAs, bioavailability abruptly declined to zero or nearly zero. On average, the decline was observed 96 days after the start of dosing, but the time of onset varied widely. In a post hoc evaluation, 234 of 3499 (6.7%) participants had this effect observed. ADAs and NAbs did not influence LDL-C response beyond the effect on bococizumab concentration (data not shown).

The magnitude of the residual errors for both PK and PD were lower for the phase I studies than for the phase II and III studies. The final PK/PD model goodness-of fit plots and VPC confirmed the appropriateness of the final model versus other models tested (Figures 2–5).

DISCUSSION

With an increasing number of antibody-based therapeutics being approved for clinical use, improved understanding of the potential effect of ADAs on the PK and/or PK/PD of biotherapeutics is important to help elucidate how immunogenicity impacts PK and efficacy, as this information is not always published alongside data on efficacy.[27] Despite bococizumab being discontinued from clinical development in 2016,[21] a large database of clinical observations is available for PK/PD analysis. As such, the objective of this modeling effort was to provide a better understanding of the PK/PD relationship of bococizumab including the onset and offset of LDL-C response, potential effects of immunogenicity, and of statins. Therefore, the results of such an analysis may be informative to other biotherapeutics under development, especially if immunogenicity is observed during clinical trials.

The population PK analysis of bococizumab data from 16 clinical studies indicated that a two-compartment model with parallel linear and MM elimination and first-order absorption adequately described the observed bococizumab PK data. Whereas the VPC plots indicate a minor over-prediction of the median bococizumab drug concentrations, this discrepancy is relatively small compared to the large intersubject variability observed in the study. Additionally, the indirect response model with stimulation of LDL-C degradation, which is consistent with the mechanism of action, well describes the time course of LDL-C response following bococizumab treatment. Consistent with known effects of statins, bococizumab clearance was increased and the first-order degradation rate for LDL-C was also increased. ADAs and NAbs had no direct effect on LDL-C response subsequent to the increased effect of ADAs on bococizumab clearance and decreased s.c. bioavailability.

In the current analysis, bococizumab PK disposition parameters – such as absorption rate estimated to be 0.151 day^{-1}, corresponding to an absorption half-life of 4.59 days – were consistent with that reported previously for bococizumab using data from phase I and II clinical

TABLE 1 Final population PK/PD parameter estimates.

PK/PD parameter		Estimate	% RSE	95% CI	Variability (CV)	Shrinkage (%)
k_a (1/day)	θ_1	0.151	1.73	0.146, 0.156		
CL (L/day)	θ_2	0.227	3.65	0.211, 0.243		
V_C (L)	θ_3	2.38	2.08	2.28, 2.47		
Q (L/day)	θ_4	0.335	2.35	0.319, 0.35		
V_P (L)	θ_5	1.95	1.84	1.88, 2.02		
V_{max} (μg/mL/day)	θ_6	2.04	4.30	1.86, 2.21		
K_M (μg/mL)	θ_7	12.5	3.55	11.6, 13.3		
F_{SC}	θ_8	0.411	2.38	0.392, 0.43		
CL_{WT}	θ_9	1.15	5.11	1.04, 1.27		
$V_{c,WT}$	θ_{10}	0.854	5.90	0.755, 0.952		
$V_{P,WT}$	θ_{11}	0.510	9.50	0.415, 0.604		
$k_{a,AGE}$	θ_{12}	−0.607	5.49	−0.672, −0.541		
Q_{AGE}	θ_{13}	−1.45	3.87	−1.56, −1.34		
$V_{max,BMI}$	θ_{14}	0.0957	18.7	0.0606, 0.131		
$F_{SC,BMI}$	θ_{15}	−0.212	20.2	−0.295, −0.128		
$V_{max,statin}$	θ_{16}	1.17	2.40	1.12, 1.23		
$F_{SC,single\text{-}dose}$	θ_{17}	1.43	1.91	1.37, 1.48		
$P_{mixture\text{-}2}$	θ_{18}	0.115	8.50	0.0956, 0.134		
T_{50}	θ_{19}	96.0	14.5	68.8, 123		
CL_{ADA}	θ_{20}	0.0658	8.66	0.0546, 0.077		
$F_{SC,ADA}$	θ_{21}	0.0512	10.2	0.041, 0.0615		
σ_{prop}	θ_{22}	0.265	1.03	0.259, 0.27		
σ_{add} (μg/mL)	θ_{23}	0.186	1.19	0.182, 0.191		
$\sigma_{phase\text{-}1}$	θ_{24}	0.401	2.45	0.381, 0.42		
$\sigma_{phase\text{-}2}$	θ_{25}	0.532	4.01	0.49, 0.574		
ω^2_{KA}	Ω_{11}	0.108	5.08	0.0972, 0.119	0.329	31.4
ω^2_{CL}	Ω_{22}	0.212	5.90	0.187, 0.237	0.460	38.1
ω^2_{Vc}	Ω_{33}	0.190	4.92	0.172, 0.208	0.436	27.7
ω^2_{Q}	Ω_{44}	0.0882	13.5	0.0648, 0.112	0.297	63.2
ω^2_{Vp}	Ω_{55}	0.0427	8.69	0.0354, 0.05	0.207	57.1
ω^2_{Vmax}	Ω_{66}	0.0486	16.0	0.0334, 0.0638	0.220	61.1
ω^2_{Fsc}	Ω_{77}	0.0615	7.77	0.0521, 0.0709	0.248	36.0
ω^2_{T50}	Ω_{88}	1.41	13.4	1.04, 1.78	1.19	16.8
ω^2_{ADA-CL}	Ω_{99}	2.02	7.19	1.74, 2.3	1.42	76.0
$\omega^2_{ADA-Fsc}$	$\Omega_{10,10}$	2.74	7.86	2.32, 3.16	1.66	75.2
ω^2_{ε}	$\Omega_{11,11}$	0.191	2.32	0.182, 0.2	0.437	−0.8
σ^2	Σ_{11}	1	Fixed	Fixed	1	6.6
k_{syn}	θ_{26}	12.4	1.47	12.1, 12.8		
γ	θ_{27}	4.78	1.71	4.62, 4.94		
E_{max}	θ_{28}	1.27	2.31	1.21, 1.32		
$E_{max,statin}$	θ_{29}	1.68	2.33	1.6, 1.75		
$E_{max,Asian}$	θ_{30}	1.36	3.89	1.26, 1.47		
$E_{max,male}$	θ_{31}	1.36	2.02	1.31, 1.41		
$E_{max,PKETA\text{-}CL}$	θ_{32}	0.689	4.6	0.627, 0.751		

TABLE 1 (Continued)

PK/PD parameter		Estimate	% RSE	95% CI	Variability (CV)	Shrinkage (%)
EC_{50}	θ_{33}	3.34	0.944	3.28, 3.4		
$EC_{50,\text{LDL-baseline}}$	θ_{34}	0.413	6.16	0.363, 0.463		
$EC_{50,\text{low-dose}}$	θ_{35}	0.687	2.76	0.65, 0.724		
$EC_{50,\text{max-T}}$	θ_{36}	1.92	25.3	0.969, 2.88		
$EC_{50,\text{T50-T}}$	θ_{37}	2590	28.7	1140, 4040		
$\sigma_{\text{LDL,prop}}$	θ_{38}	0.0986	1.52	0.0957, 0.102		
$\sigma_{\text{LDL,add}}$	θ_{39}	9.55	1.19	9.33, 9.78		
$\sigma_{\text{LDL,phase-1}}$	θ_{40}	0.726	2.78	0.686, 0.766		
ω^2_{Ksyn}	$\Omega_{12,12}$	0.331	3.59	0.308, 0.354	0.575	22.4
ω^2_{Emax}	$\Omega_{13,13}$	0.235	3.24	0.22, 0.25	0.485	18.1
ω^2_{EC50}	$\Omega_{14,14}$	0.0609	5.91	0.0538, 0.068	0.247	38.8
$\omega^2_{\text{max-T}}$	$\Omega_{15,15}$	2.33	4.54	2.13, 2.54	1.53	37.1
$\sigma_{\text{LDL},\varepsilon}$	$\Omega_{16,16}$	0.219	2.8	0.207, 0.231	0.468	0.4
Σ	Σ_{11}	1		Fixed	1	1.4

Abbreviations: CI, confidence interval; CL, clearance; CV, coefficient of variation; EC_{50}, half maximal effective concentration; E_{max}, maximum effect; PD, pharmacodynamic; PK, pharmacokinetic; RSE, relative standard error; V_{max}, maximal rate of metabolism.

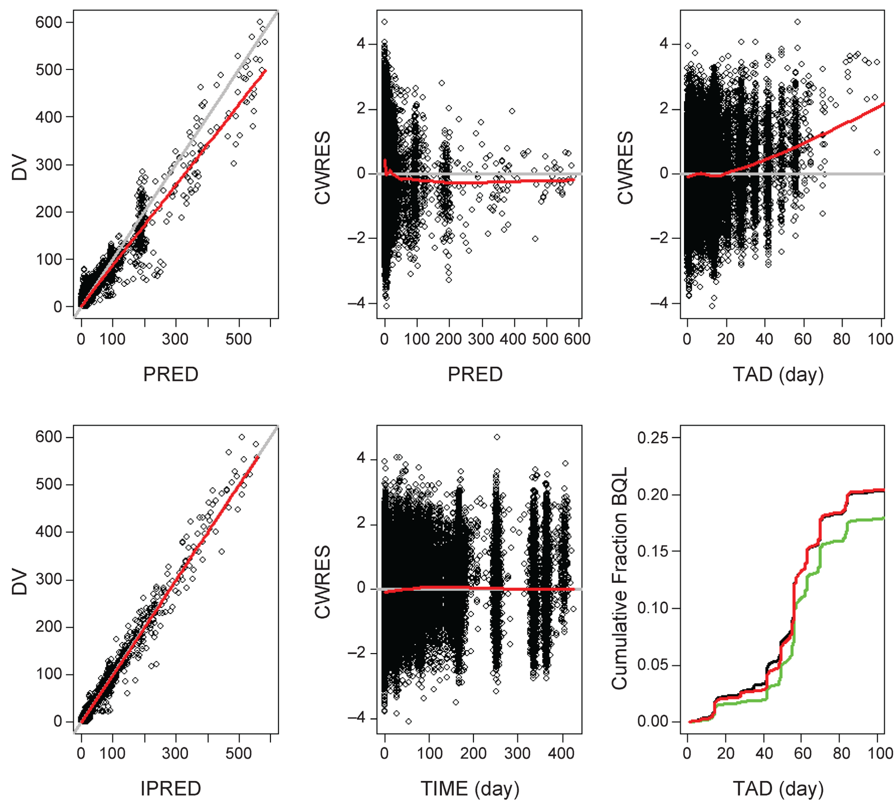

FIGURE 2 Final PK model goodness-of-fit plots. The gray $y = x$ or $y = 0$ lines are included for reference. The bold red lines are the LOWESS (local regression smoother) trend lines. Bottom right plots show cumulative fraction of observations (black), individual predictions (green), and population predictions (red) below the quantification limit. BQL, below the quantification limit; CWRES, conditional weighted residuals; DV, observed bococizumab concentrations; IPRED, individual predicted bococizumab concentrations; PK, pharmacokinetic; PRED, population predicted bococizumab concentrations; TAD, time after the most recent dose; TIME, time after the first dose.

studies,[13] and with data from the two approved anti-PCSK9 mAbs alirocumab and evolocumab.[22,23] However, the estimated s.c. bioavailability for bococizumab (41%) was lower than those reported for alirocumab (57%)[39] and evolocumab (72%).[40] For mAbs, the development of ADAs and NAbs can potentially impact their PK, with dose and duration of therapy.[41] In our analysis of bococizumab, the presence of ADAs increased bococizumab CL and decreased s.c. bioavailability, with the effects proportional to the exponent of the observed ADA titers. In 11.5% of patients, bioavailability abruptly declined to approximately zero, with the decline observed ~96 days after dosing initiation. We accommodated this observation by the implementation of a mixture model identifying this subset of

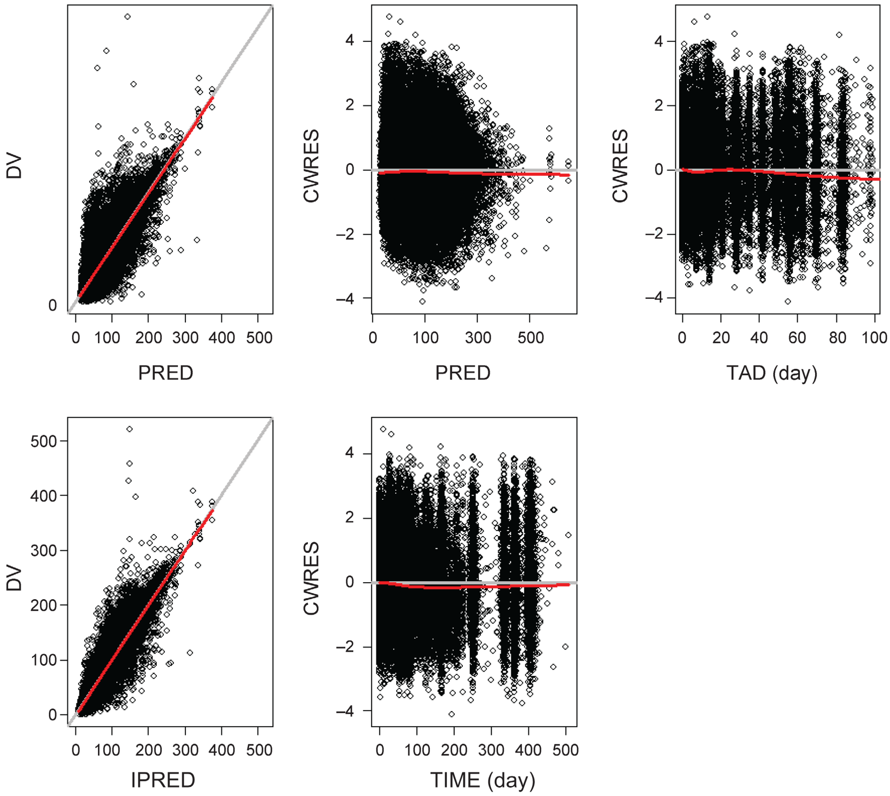

FIGURE 3 Final PK/PD model goodness-of-fit plots. The gray $y=x$ or $y=0$ lines are included for reference. The bold red lines are the LOWESS (local regression smoother) trend lines. CWRES, conditional weighted residuals; DV, observed LDL-C concentrations; IPRED, individual predicted LDL-C concentrations; PD, pharmacodynamic; PK, pharmacokinetic; PRED, population predicted LDL-C concentrations; TAD, time after the most recent dose; TIME, time after the first dose.

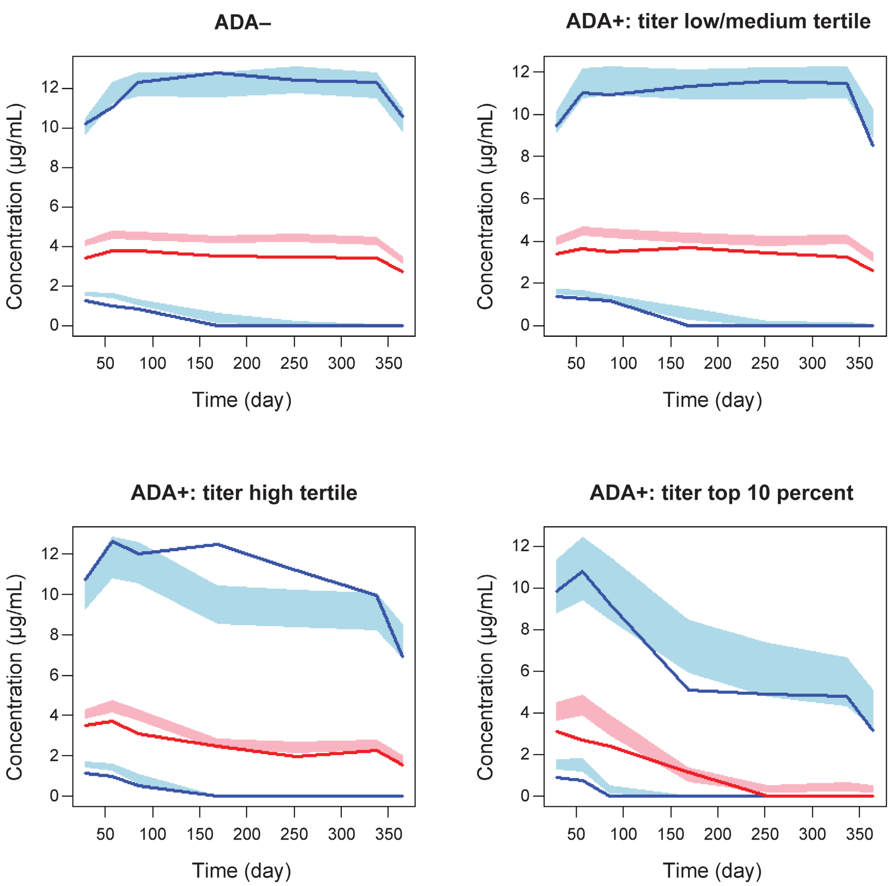

FIGURE 4 Visual predictive check of final PK model: bococizumab concentration–time profiles, by ADA titer tertile. The lines show median (red), and the 10th and 90th percentiles (blue) of the observed bococizumab concentrations for the four 1-year studies (150 mg q2w). The shaded regions show the 80% confidence intervals on these quantities obtained by simulations. ADA, anti-drug antibody; PK, pharmacokinetic; q2w, every 2 weeks.

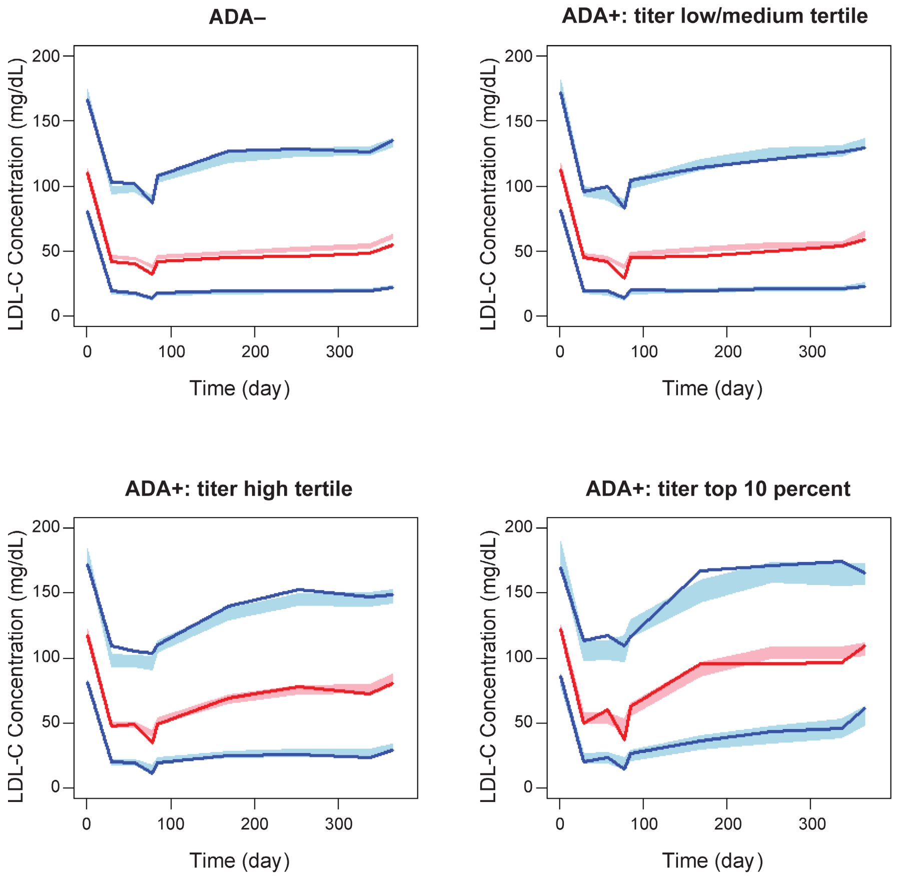

FIGURE 5 Visual predictive check of final PK/PD model. LDL-C concentration versus time, by ADA titer tertile. The lines show median (red), and the 10th and 90th percentiles (blue) of the observed LDL-C values from the four 1-year studies (150 mg q2w). The shaded regions show the 80% confidence intervals on these quantities obtained by simulations. ADA, anti-drug antibody; LDL-C, low-density lipoprotein cholesterol; PD, pharmacodynamic; PK, pharmacokinetic; q2w, every 2 weeks.

individuals. It is speculated this abrupt decline in bioavailability might be consistent with nonadherence to dosing.

Inclusion of the phase III SPIRE clinical trial data allowed modeling of the LDL-C response in the presence and absence of statins, as well as for participants who developed ADAs and NAbs.[42] We observed that co-administration of statins increased target-mediated maximum elimination rate V_{max} of bococizumab by 17%. This is consistent with the effect of statins (stimulation of LDL-R and PCSK9 production[43–46]) and target-mediated elimination of bococizumab (via binding to PCSK9[1,35]). Therefore, upregulation of PCSK9 could have resulted in LDL-C increase, but the effect of upregulating LDL-R exceeded the effect of up-regulation of PCSK9, suggesting net enhancement of LDL-C reduction. Indeed, an increase in E_{max} was estimated from the population PK/PD model, mediated through k_{deg} for LDL-C, and proportional to PKETA2. The estimated effect of statins on bococizumab PK is also consistent with the reported statin effects on alirocumab and evolocumab PK.[39,40]

Bococizumab clinical development was discontinued due in part to unexpected higher incidence of ADAs and attenuation of LDL-C efficacy with time.[21] Whereas ADAs were measured in phase II trials in participants with hypercholesterolemia,[11,12,18] the clinical impacts of ADAs on bococizumab exposure and LDL-C lowering efficacy were not evident until longer-term data from the large phase III studies were available.[15] Although earlier clinical data were not predictive of long-term impact of ADAs on PK and efficacy, this was partly confounded by (1) a less sensitive and drug-tolerant ELISA ADA assay was used to support early clinical studies, while a more sensitive and drug-tolerant bridging ECL ADA assay was developed during phase III clinical development; and (2) the downward titration design of the 24-week phase IIb study may have further confounded the ability to detect the impact of ADAs and/or NAbs on bococizumab efficacy. However, these earlier clinical data did provide a hint of potential effect of ADAs on bococizumab efficacy, as a small number of participants reported loss of LDL-C efficacy across the four phase II studies.[11,12,18] As such, it is prudent for all biotherapeutic programs to develop a fit-for-purpose drug- and target-tolerant ADA assay at the onset of the clinical program to appropriately assess the clinical impact of immunogenicity on PK, PD, efficacy, and/or safety. Whereas it may not always be feasible to incorporate ADA and/or NAb data in early population PK/PD analysis due to the potentially small number of ADA-positive participants in the overall PK/PD dataset, early evaluation of the clinical impact of ADAs on PK, PD, efficacy, and safety could potentially flag the immunogenicity risk of a biotherapeutic and further inform drug development strategy. If immunogenicity signals emerge from early clinical program, one could potentially stagger phase III studies in order to appropriately direct clinical development.

One perceived limitation of the PK/PD model is that it is based on a MM approximation of a target-mediated drug disposition (TMDD) model. However, as demonstrated through diagnostic and VPC plots, the MM approximation of a TMDD model adequately described bococizumab and LDL-C concentrations. Additionally, there was an apparent increase in EC_{50} over time, suggesting a decreased efficiency in LDL-C elimination. This increased EC_{50} is consistent with the loss of durability reported in the SPIRE trials,[15] even in participants who were ADA negative. The incorporation of time-dependent EC_{50} captured this apparent LDL-C response and resulted in better fit of data. Further, a dose effect on EC_{50} was implemented in order to provide a better description of the observed individual data. It is acknowledged this is rather empirical, however, despite considerable efforts, we were not successful in incorporating a mechanistic expression to account for the observed data. An additional limitation of the study is that while a mixture model was implemented to account for the abrupt drop in bococizumab exposure, the reason for this observation is unknown. It is possible this could be due to treatment noncompliance as the rate of injection site reaction was 12.7 per 100 person-years in bococizumab-treated participants across the six phase III studies.[15] Alternatively, this could be due to ADAs impacting bococizumab exposure in the subset of participants who were ADA positive. Consistent with the observed PK data, wide variation in LDL-C response was observed in both ADA-positive and ADA-negative participants in the phase III studies.[15]

CONCLUSION

A two-compartment model with parallel linear and nonlinear elimination, and the MM approximation of a TMDD model adequately described the observed bococizumab concentration data and LDL-C reduction. Consistent with the mechanism, co-administration of statins increased the maximum effect of bococizumab and the magnitude of the increased LDL-C lowering was proportional to the random effect on bococizumab clearance. Although the impact of ADAs and NAbs on PK and PD was explored, increased bococizumab clearance due to ADAs sufficiently described the observed changes in bococizumab concentration and LDL-C response over time. These observations add to the known literature of PCSK9 inhibitors and enhance the understanding of the influence of immunogenicity on the PK/PD of mAbs.

AUTHOR CONTRIBUTIONS

All authors contributed to writing the manuscript. E.Q.W., D.P., C.Y., and K.S. designed the research. E.Q.W., D.P., and C.Y. performed the research. N.K., L.G., and K.S. analyzed the data.

ACKNOWLEDGMENTS

Medical writing support was provided by Karen Burrows, MPhil, CMPP, of Engage Scientific (Horsham, UK) and was funded by Pfizer.

FUNDING INFORMATION

This study was sponsored by Pfizer.

CONFLICT OF INTEREST STATEMENT

Ellen Q. Wang and Carla Yunis are full-time employees of and hold stock options in Pfizer. David Plowchalk, Nitin Kaila, and Kevin Sweeney were employees of Pfizer at the time the study was conducted. Leonid Gibiansky was a paid consultant to Pfizer in relation to the study conduct.

DATA AVAILABILITY STATEMENT

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

ORCID

Nitin Kaila https://orcid.org/0009-0002-6351-5178
Leonid Gibiansky https://orcid.org/0000-0001-6005-7760

REFERENCES

1. Liang H, Chaparro-Riggers J, Strop P, et al. Proprotein convertase substilisin/kexin type 9 antagonism reduces low-density lipoprotein cholesterol in statin-treated hypercholesterolemic nonhuman primates. *J Pharmacol Exp Ther*. 2012;340:228-236.
2. Goldstein JL, Brown MS. The LDL receptor. *Arterioscler Thromb Vasc Biol*. 2009;29:431-438.
3. Lagace TA, Curtis DE, Garuti R, et al. Secreted PCSK9 decreases the number of LDL receptors in hepatocytes and in livers of parabiotic mice. *J Clin Invest*. 2006;116:2995-3005.
4. Stein EA. What role will proprotein convertase subtilisin/kexin type 9 inhibitors play in hyperlipidemia management? *Curr Opin Endocrinol Diabetes Obes*. 2016;23:97-105.
5. Scherer DJ, Nelson AJ, Psaltis PJ, Nicholls SJ. Targeting low-density lipoprotein cholesterol with PCSK9 inhibitors. *Intern Med J*. 2017;47:856-865.
6. Guardiola M, Plana N, Ibarretxe D, et al. Circulating PCSK9 levels are positively correlated with NMR-assessed atherogenic dyslipidaemia in patients with high cardiovascular risk. *Clin Sci (Lond)*. 2015;128:877-882.

7. Li S, Guo YL, Xu RX, et al. Association of plasma PCSK9 levels with white blood cell count and its subsets in patients with stable coronary artery disease. *Atherosclerosis*. 2014;234:441-445.
8. Zhou Y, Chen W, Lu M, Wang Y. Association between circulating proprotein convertase subtilisin/kexin type 9 and major adverse cardiovascular events, stroke, and all-cause mortality: systemic review and meta-analysis. *Front Cardiovasc Med*. 2021;8:617249.
9. Del Pinto R, Grassi D, Properzi G, Desideri G, Ferri C. Low density lipoprotein (LDL) cholesterol as a causal role for atherosclerotic disease: potential role of PCSK9 inhibitors. *High Blood Press Cardiovasc Prev*. 2019;26:199-207.
10. Duprez DA, Handelsman Y, Koren M. Cardiovascular outcomes and proprotein convertase subtilisin/kexin type 9 inhibitors: current data and future prospects. *Vasc Health Risk Manag*. 2020;16:403-418.
11. Ballantyne CM, Neutel J, Cropp A, et al. Results of bococizumab, a monoclonal antibody against proprotein convertase subtilisin/kexin type 9, from a randomized, placebo-controlled, dose-ranging study in statin-treated subjects with hypercholesterolemia. *Am J Cardiol*. 2015;115:1212-1221.
12. Fazio S, Robertson DG, Joh T, et al. Effects of 12 weeks of treatment with intravenously administered bococizumab, a humanized monoclonal antibody blocking proprotein convertase subtilisin/kexin type 9, in hypercholesterolemic subjects on high-dose statin. *Cardiovasc Ther*. 2018;36:e12308. doi:10.1111/1755-5922.12308
13. Gumbiner B, Joh T, Liang H, et al. The effects of single- and multiple-dose administration of bococizumab (RN316/PF-04950615), a humanized IgG2Deltaa monoclonal antibody binding proprotein convertase subtilisin/kexin type 9, in hypercholesterolemic subjects treated with and without atorvastatin: results from four phase I studies. *Cardiovasc Ther*. 2018;36:e12309. doi:10.1111/1755-5922.12309
14. Ridker PM, Rose LM, Kastelein JJP, et al. Cardiovascular event reduction with PCSK9 inhibition among 1578 patients with familial hypercholesterolemia: results from the SPIRE randomized trials of bococizumab. *J Clin Lipidol*. 2018;12:958-965.
15. Ridker PM, Tardif JC, Amarenco P, et al. Lipid-reduction variability and antidrug-antibody formation with bococizumab. *N Engl J Med*. 2017;376:1517-1526.
16. Wang EQ, Plotka A, Salageanu J, et al. Comparative pharmacokinetics and pharmacodynamics of bococizumab following a single subcutaneous injection using drug substance manufactured at two sites or administration via two different devices. *Clin Pharmacol Drug Dev*. 2019;8:40-48.
17. Wang EQ, Plotka A, Salageanu J, Sattler C, Yunis C. Pharmacokinetics and pharmacodynamics of bococizumab, a monoclonal antibody to PCSK9, after single subcutaneous injection at three sites [NCT 02043301]. *Cardiovasc Ther*. 2017;35:e12278. doi:10.1111/1755-5922.12278
18. Yokote K, Kanada S, Matsuoka O, et al. Efficacy and safety of bococizumab (RN316/PF-04950615), a monoclonal antibody against proprotein convertase subtilisin/kexin type 9, in hypercholesterolemic japanese subjects receiving a stable dose of atorvastatin or treatment-naive-results from a randomized, placebo-controlled, dose-ranging study. *Circ J*. 2017;81:1496-1505.
19. Ridker PM, Revkin J, Amarenco P, et al. Cardiovascular efficacy and safety of bococizumab in high-risk patients. *N Engl J Med*. 2017;376:1527-1539.
20. Wang EQ, Bukowski JF, Yunis C, et al. Assessing the potential risk of cross-reactivity between anti-bococizumab antibodies and other anti-PCSK9 monoclonal antibodies. *BioDrugs*. 2019;33:571-579.
21. Pfizer Inc. Pfizer discontinues global development of bococizumab, its investigational PCSK9 inhibitor. Accessed December 5, 2022. www.pfizer.com/news/press-release/press-release-detail/pfizer_discontinues_global_development_of_bococizumab_its_investigational_pcsk9_inhibitor
22. Sanofi. PRALUENT™ (alirocumab) prescribing information. Accessed September 19, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125559Orig1s000lbledt.pdf
23. Amgen. REPATHA™ (evolocumab) U.S. Prescribing information. Accessed September 19, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125522s000lbl.pdf
24. Foltz IN, Karow M, Wasserman SM. Evolution and emergence of therapeutic monoclonal antibodies: what cardiologists need to know. *Circulation*. 2013;127:2222-2230.
25. van Brummelen EM, Ros W, Wolbink G, Beijnen JH, Schellens JH. Antidrug antibody formation in oncology: clinical relevance and challenges. *Oncologist*. 2016;21:1260-1268.
26. Nelson AL, Dhimolea E, Reichert JM. Development trends for human monoclonal antibody therapeutics. *Nat Rev Drug Discov*. 2010;9:767-774.
27. Wang YM, Wang J, Hon YY, Zhou L, Fang L, Ahn HY. Evaluating and reporting the immunogenicity impacts for biological products-a clinical pharmacology perspective. *AAPS J*. 2016;18:395-403.
28. Vincent FB, Morand EF, Murphy K, Mackay F, Mariette X, Marcelli C. Antidrug antibodies (ADAb) to tumour necrosis factor (TNF)-specific neutralising agents in chronic inflammatory diseases: a real issue, a clinical perspective. *Ann Rheum Dis*. 2013;72:165-178.
29. Thomas SS, Borazan N, Barroso N, et al. Comparative immunogenicity of TNF inhibitors: impact on clinical efficacy and tolerability in the management of autoimmune diseases. A systematic review and meta-analysis. *Biodrugs*. 2015;29:241-258.
30. Bartelds GM, Krieckaert CL, Nurmohamed MT, et al. Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. *JAMA*. 2011;305:1460-1468.
31. Reinhold I, Blümel S, Schreiner J, et al. Clinical relevance of anti-tnf antibody trough levels and anti-drug antibodies in treating inflammatory bowel disease patients. *Inflamm Intest Dis*. 2021;6:38-47.
32. Ara-Martin M, Pinto PH, Pascual-Salcedo D. Impact of immunogenicity on response to anti-TNF therapy in moderate-to-severe plaque psoriasis: results of the PREDIR study. *J Dermatolog Treat*. 2017;28:606-612.
33. Ridker PM, Amarenco P, Brunell R, et al. Evaluating bococizumab, a monoclonal antibody to PCSK9, on lipid levels and clinical events in broad patient groups with and without prior cardiovascular events: rationale and design of the studies of PCSK9 inhibition and the reduction of vascular events (SPIRE) lipid lowering and SPIRE cardiovascular outcomes trials. *Am Heart J*. 2016;178:135-144.
34. Kaila N, Wang EQ, Sweeney K, Plowchalk D. Model-based meta-analysis of the clinical efficacy of anti-PCSK9 (proprotein

convertase subtilisin kexin type 9) monoclonal antibodies. *Clin Pharmacol Ther*. 2015;97:S21-S56.
35. Udata C, Garzone PD, Gumbiner B, et al. A mechanism-based pharmacokinetic/pharmacodynamic model for bococizumab, a humanized monoclonal antibody against proprotein convertase subtilisin/kexin type 9, and its application in early clinical development. *J Clin Pharmacol*. 2017;57:855-864.
36. Wang EQ, Plowchalk D, Gibiansky L, Sweeney K, Kaila N. Population pharmacokinetic and pharmacodynamic modeling of bococizumab (RN316/PF-04950615) in hypercholesterolemic subjects. European atherosclerosis society. Madrid, Spain, 31 May-3 June, 2014. Abstract 927 .
37. Boxenbaum H. Interspecies pharmacokinetic scaling and the evolutionary-comparative paradigm. *Drug Metab Rev*. 1984;15:1071-1121.
38. Beal SL. Ways to fit a PK model with some data below the quantification limit. *J Pharmacokinet Pharmacodyn*. 2001;28:481-504.
39. Djebli N, Martinez JM, Lohan L, et al. Target-mediated drug disposition population pharmacokinetics model of alirocumab in healthy volunteers and patients: pooled analysis of randomized phase i/ii/iii studies. *Clin Pharmacokinet*. 2017;56:1155-1171.
40. Gibbs JP, Doshi S, Kuchimanchi M, et al. Impact of target-mediated elimination on the dose and regimen of evolocumab, a human monoclonal antibody against proprotein convertase subtilisin/kexin type 9 (PCSK9). *J Clin Pharmacol*. 2017;57:616-626.
41. Sethu S, Govindappa K, Alhaidari M, Pirmohamed M, Park K, Sathish J. Immunogenicity to biologics: mechanisms, prediction and reduction. *Arch Immunol Ther Exp (Warsz)*. 2012;60:331-344.
42. Ryman JT, Meibohm B. Pharmacokinetics of monoclonal antibodies. *CPT Pharmacometrics Syst Pharmacol*. 2017;6:576-588.
43. Chan ML, Shiu SW, Cheung CL, Yu-Hung Leung A, Tan KC. Effects of statins on the inducible degrader of low-density lipoprotein receptor in familial hypercholesterolemia. *Endocr Connect*. 2022;11:e220019.
44. Mayne J, Dewpura T, Raymond A, et al. Plasma PCSK9 levels are significantly modified by statins and fibrates in humans. *Lipids Health Dis*. 2008;7:22.
45. Kuyama N, Kataoka Y, Takegami M, et al. Circulating mature PCSK9 level predicts diminished response to statin therapy. *J Am Heart Assoc*. 2021;10:e019525.
46. Welder G, Zineh I, Pacanowski MA, Troutt JS, Cao G, Konrad RJ. High-dose atorvastatin causes a rapid sustained increase in human serum PCSK9 and disrupts its correlation with LDL cholesterol. *J Lipid Res*. 2010;51:2714-2721.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wang EQ, Kaila N, Plowchalk D, Gibiansky L, Yunis C, Sweeney K. Population PK/PD modeling of low-density lipoprotein cholesterol response in hypercholesterolemic participants following administration of bococizumab, a potent anti-PCSK9 monoclonal antibody. *CPT Pharmacometrics Syst Pharmacol*. 2023;12:2013-2026. doi:10.1002/psp4.13050